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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,096	11/19/2001	Anke Rattenholl	1406/415	2974

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EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/807,096	RATTENHOLL ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,20 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,20 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 6/19/08 has been entered.

2. The rejection of claims 8, 10 & 27-28 under 35 U.S.C. 112, first paragraph for new matter is withdrawn due to the cancellation of the claims, or due to Applicants' arguments.

3. The rejection of claims 8, 20 & 27-28 under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete are withdrawn due to the amendment of base claim 8.

4. Applicant's arguments filed 6/19/08 have been fully considered but they are not deemed to be persuasive.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 26 & 29 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper No: 20080212, and as follows. This is a new matter rejection.

Applicants argue on pages 5-7 of the response that "the instant specification describes purifying, solubilizing, refolding, and ion-exchange purification of the inclusion body material to generate biologically active rh proNGF", and then refers to page 16 of the specification, which refers to Figure 2. In this regard, the purity limitation of "at least 90% purity" is persuasive (i.e., as it relates to claim 8).

Second, Applicants argue on pages 8-9 of the response that "an EC50 value represents a measure of biological activity". The Examiner agrees. Applicants then argue how calculation of the EC 50 value relates to the "biological activites of rh proNGF and rh β-NGF, [and that] the corresponding molecular weights of these polypeptides must be considered." However, in contrast to Applicants' calculations for this single comparison of values, and using Applicants' example of rh proNGF being 1.84 times massive as rh β-NGF, and the EC50 of rh β-NGF as 0.369, a measurement of 50% activity would be (0.369 / 1.84) (0.50) = 0.100 ng/ml, not the disclosed 0.106 ng/ml. Although this number is technically "less than about twice that of rh β-NGF on a molar basis", this is different in concept than a value of 0.100 ng/ml, because 0.100 ng/ml does not represent a range of values "less than about twice", as represented by the current claims. Again, the sole described EC50 value of 0.369 ng/ml versus 0.106 ng/ml" in a DRG assay does not reasonably extrapolate to "an EC50 value… that is *less than about twice* that of human β-NGF on a molar basis", as now claimed, even after correcting "a typographical error [in claim 26]"; thereby, still constituting new matter similar to that previously made of record for claim 26.

7. Claims 26 & 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons similar to that made of record in Paper No: 20080212.

The recitation of "*less than about twice*" is indefinite because the limitation of "about" normally means $\pm$ 5%, etc. while the limitation of "less than" removes any upper limit above "twice"; thereby, being contradictory.

8. Claims 8, 20 & 26-29 are rejected under 35 U.S.C. 102(b) as anticipated by Edwards et al (U.S. Patent 5,683,894), and as described on page 4 of the specification where Edward's is acknowledged as admitted prior art for describing the "whole prosequence", and for the reasons made of record in Paper NOs: 20050124, 20050706, 20060329, 20060913 & 20080212, and as follows.

Applicants argue on pages 10-14 of the response that Edwards fails to teach "a pharmaceutical composition comprising purified human proNGF…", and then pick and choose passages within Edwards to support their supposition, followed by making unsubstantiated assertions that "*in vitro* translated proNGF, even if it were purified to at least 90% purity, would be expected to have any biological activity at all …", which ignores U.S. case law previously made of record, and MPEP 2123, which again states:

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also >*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component);<Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

Thus, Applicants' arguments remain not persuasive.

In summary, Edwards et al teach how to make a pharmaceutical composition comprising a recombinant pro-NGF-beta solution "derived from humans" (e.g., col. 4, lines 40-42), which inherently comprises SEQ ID NO: 4 and inherently is encoded by a nucleic acid comprising SEQ ID NO: 3 (i.e., as it relates to claims 20, 27, 28 & 29). In that Example 2 (col. 7) teaches *in vitro* translated proNGF (i.e., including proNGF from "*human*, murine, bovine; col. 4, line 41), which therefore would reasonably be purified to least 90% purity based on this translation system, the limitations of claim 8 are anticipated; absent evidence to the contrary. In that proNGF produced by such a procedure inherently has whatever activity it possesses based on its structural characteristics, the limitations of claims 26 & 29 are also reasonably met.

In arguendo, no product-by-process steps are recited in the current claims. Even if such steps were recited, the issue would then become that if the product in a product-by-process claim (i.e., proNGF) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). It has further been established by the courts that a product (i.e., the proNGF product) inherently possesses

characteristics of that product (i.e., possesses any activity inherent to the protein which is derived from its amino acid sequence), and that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

The court in *In re Crish*, 73 USPQ2d 1364 (Fed. Cir. 2004), also held that "… the [further] identification and characterization of a [previously known] prior art material… does not make it novel".

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

9. Claims 8, 20 & 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray & Ullrich (U.S. Patent 5,169,762) and Collins et al (U.S. Patent 5,235043), for the reasons made of record in Paper No: 20080212, and as follows.

Applicants argue on pages 14-17 of the response that "[i]nherency, however, may not be established by probabilities or possibilities…" and cites MPEP 2163.07(a). However, this rejection is a rejection under 103, and not under 102, where a *prima facie* case of obviousness has clearly been established. Applicants then argue that "Edwards explicitly discloses that *in vitro* translated and recombinant forms of proNGF have no activity, [and] as a result, there is believed to be clear scientific evidence in the record that biological activity for proNGF is not an

inherent property based merely on primary structure", and that "[g]iven the fact that the prior art of record has established that recombinant and *in vitro* forms of proNGF do not necessarily have biological activity, the Collins reference, like the Gray & Ullrich, does not satisfy the requirements of inherent disclosure", which is simply is a misrepresentation of the record. In contrast to Applicants' assertions, the state of the art is such that polypeptides made recombinantly in *E. coli* normally result in inclusion bodies with reduced activity that subsequently require denaturing and refolding using methods well known in the art, which is the method Applicants use to make their polypeptides, but which is not claimed. As also previously made of record, just because Edwards et al state in their Example 6 (i.e., using recombinant expression of *murine* proNGF in mouse L929 cells) that "supernatant from L929/VV:wt exhibited no NGF activity (i.e., control supernatant), supernatant from L929/VV:NGF-A and L929/W:NGF-B (not digested) exhibited little or no activity [when compared to cleaved/ processed *murine* NGF], and supernatant from L929/VV:NGF-A and L929/W:NGF-B digested with trypsin exhibited substantial NGF-beta activity", this has nothing to do with whether "*in vitro* translated human pro-NGF protein has no activity, as assumed by Applicants, because in *vitro* translated pro-NGF was not use in Edwards' Example 6. Nor does Applicants' mischaracterization of the teachings of Edwards negate over 30 years of recombinant production of active polypeptides in eukaryotic cells, which is well known in the art to avoid the problem of correct folding of polypeptides. As far as *in vitro* production of polypeptides, this is also routinely done in the art (e.g., as illustrated by the *in vitro* translation kits available from a number of companies), where nothing in the record previously questioned or suggested that *in vitro* translated polypeptides are inactive, in contrast to Applicants' assertions. Nevertheless, the

record is clear, which is further based on U.S. case law, that it is reasonable that a product possesses the same functional characteristics derived from its structure (i.e., amino acid sequence), in which pro-NGF is still pro-NGF is still pro-NGF, regardless of what further characterization/mechanisms of action are discovered 9 years after the claimed priority date of the instant invention (i.e., as in Exhibit D), 6 years after the claimed priority date (i.e., as in Exhibit E), or 10 years after the claimed invention (i.e., 10/9/98) as in Exhibit F. Moreover, Applicants' arguments on pages 16-17 of the response that proNGF is different, is further contradicted by their eventual acknowledgement that "endocytosis and cleavage of pro-neurotrophins [including proNGF] produce processed forms of neurotrophins [i.e., β-NGF] that are capable of inducing Trk Activation [i.e., the high affinity NGF receptor]". Thereby, also supporting the prodrug argument made of record in the previous Office action, and providing additional motivation to combine the teachings of Gray et al with Collins et al. Thus, Applicants' arguments are not found persuasive.

Applicants are also reminded of that held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., proNGF for NGF] for another to obtain predictable results [i.e., increase DRG neuronal survival], or the combining of prior art elements [i.e., Collins' proneurotrophin polypeptides for the proNGF polypeptide] according to known methods [of making recombinant polypeptides] to yield predictable results [i.e., increase survival of DRG neurons], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e,, increased survival of DRG neurons using molecules that comprise the NGF amino acid sequence] where it would be obvious to try based on the teachings of Collins et al.

In summary, Gray et al teach both the amino acid and nucleotide sequence of human proNGF (i.e., Figs. 4-6; as it relates to claims 27-29). Gray also teach methods of making NGF proteins recombinantly using either prokaryotic or eukaryotic host cells (e.g., cols. 3-6; as it relates to claims 27 & 28), as well as pharmaceutical compositions thereof (e.g., col. 13; as it relates to claims 8, 20, 26 & 29). Although Gray et al are silent regarding the relative activity of proNGF as it relates to β-NGF, the activity of proNGF (or any polypeptide, in fact) is directly related to its structure (i.e., its amino acid sequence), and therefore, is an inherent property of proNGF (i.e., as it relates to claims 26 & 29). However, Gray et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

Collins et al teach "production of purified forms of all members of the NGF/BDNF family of neurotrophic proteins which would be valuable as pharmaceutical preparations" (e.g., col. 5), as well as biologically active recombinant human NGF family member proteins (e.g., cols. 5, 9-10, & 24; Figs. 6 & 7; as it relates to claims 8, 20 & 26-29). Although Collins et al are silent regarding the relative activity of proNGF as it relates to β-NGF, the activity of proNGF is directly related to its structure (i.e., its amino acid sequence), and therefore, is an inherent property of proNGF (i.e., as it relates to claims 26 & 29). Nevertheless, Collins et al teach that it was well accepted in the art that "the proper folding and assumption of biological activity of mature NGF will only occur if it is first synthesized as the full-length precursor (i.e., as a proneurotrophin, such as proNGF), as occurs in eukaryotic cells and in natural sources" (i.e., col. 32, lines 62-65); thereby, providing motivation for making human proNGF protein nonetheless. However, Collins et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

It would have been obvious to one of ordinary skill in the art to make and purify human proNGF to homogeneity based on the teachings of both Gray and/or Collins using standard purification techniques known in the art, or as described by both Gray et al, or by Collins et al. , etc. either for use in pharmaceutical compositions, as suggested by Collins, in which the subsequent purification would reasonably minimize undesirable side effects and/or adverse immunological concerns well known in the art (thereby, increasing the number of neurotrophic proteins valuable for treating neurodegenerative diseases, as suggested by Collins (e.g., col. 5)), or for use of human proNGF as a prodrug for its eventual processing into a biologically active and mature NGF form, whose biological activity is well characterized within the art.

In arguendo, no product-by-process steps are recited in the current claims. Even if such steps were recited, the issue would then become that if the product in a product-by-process claim (i.e., proNGF) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). It has further been established by the courts that a product (i.e., the proNGF product) inherently possesses characteristics of that product (i.e., possesses any activity inherent to the protein because of its amino acid sequence), and that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

The court in *In re Crish*, 73 USPQ2d 1364 (Fed. Cir. 2004), also held that "… the [further] identification and characterization of a [previously known] prior art material… does not make it novel".

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert C. Hayes, Ph.D./
Primary Examiner, Art Unit 1649
September 30, 2008